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## Narrowband-UVB treatment for psoriasis is highly economical and causes significant savings in cost for topical treatments

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- What's already known about this topic? NB-UVB is considered expensive. However, existing estimates of treatment costs are largely based on assumptions and do not consider treatment-associated savings.
- What does this study add? We present comprehensive direct and indirect actual cost incurred for NB-UVB by a provider serving a population of 420,000 over six years and identify significant savings achieved due to the reduced need of topical treatment. Our data necessitate a review of cost figures used in health technology appraisals.

## Abstract

**BACKGROUND:** Narrowband – UVB (NB-UVB) treatment for psoriasis is considered expensive. However, existing data are based on estimates and do not consider indirect cost savings. **OBJECTIVES:** To define actual costs of NB-UVB incurred by the service provider, as well as treatment-associated cost savings. **METHODS:** Data linkage of (i) comprehensive treatment records, (ii) prescribing data for all NB-UVB treatment episodes spanning six years in a population of 420,000. Minimisation of data fluctuation by: (a) compiling data from 4 independent treatment sites, (b) use of drug prescribing unrelated to psoriasis as negative control. **RESULTS:** NHS Tayside spent an average of £257 per NB-UVB treatment course (£257  $\pm$  63; range 150 – 286 across four independent treatment sites), contrasting sharply with the estimate of £1882 used by NICE UK. The cost of topical treatments averaged £128 per patient in the 12-months prior to NB-UVB, accounting for 42 % of overall drug costs incurred by these patients. This was reduced by 40% to £53 per patient over the 12 month period following NB-UVB treatment while psoriasis unrelated drug-prescribing remained unchanged, suggesting disease-specific effects of NB-UVB. Data were not due to

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site-specific factors as confirmed by highly similar results observed between treatment sites operated by distinct staff. Finally, we detail all staff hours directly and indirectly involved in treatment, allowing direct translation of cost into other health care systems. CONCLUSIONS: NB-UVB is a low-cost treatment; cost figures currently used in health technology appraisals are an overestimate based on the data presented here. Creating or extending access to NB-UVB is likely to offer additional savings by delaying or avoiding costly third line treatments for many patients.

## Introduction

Narrowband-UVB (NB-UVB) treatment has been shown to be effective in psoriasis in numerous clinical trials <sup>1-5</sup> and represents a cornerstone of treatment. However, the treatment has a reputation of being costly and difficult to implement. This perception is reflected in treatment guidelines, such as the most recently published British Association of Dermatology (BAD) guidelines which fail to even include NB-UVB in the biologic drug treatment pathway (recommendation R4 <sup>6</sup>).

Defining the actual full cost of a non-drug based treatment is notoriously difficult. Thus, available data on the economics of UVB rely on assumptions on factors such as staff-related or estate cost <sup>7 8</sup> rather than actual financial turnover. This is chiefly do to the difficulties in obtaining high quality data. Rather than actually incurred cost, studies tend to focus on derived constructs such as Quality-adjusted Life Years (QALY), and not on precise delineation of actual expenditure (e.g. <sup>9</sup> summarily derives phototherapy cost from the National

Health Tariffs). In addition, to the best of our knowledge, no published reports have considered the financial impact of NB-UVB associated cost savings by potentially reduced need for concomitant topical treatment following NB-UVB therapy. This lack of data is most likely due to the difficulties in retrieving comprehensive treatment records.

As detailed previously, we have electronic access to complete records of all medical prescriptions filled for a population of 420,000 across Tayside/ Perthshire/ North-East Fife in Scotland <sup>10</sup>. The population as such is marked by low demographic mobility as well as complete service provision through a single health care provider (NHS Tayside). In addition, phototherapy for the entire population is provided by one single department, dispensed at four separate treatment sites, and clinical treatment outcomes are prospectively recorded. We have most recently interrogated this comprehensive dataset to define the efficacy of NB-UVB treatment for psoriasis under real-world conditions <sup>11</sup>. These data showed that NB-UVB treatment is highly effective and leads to a significant reduction in topical cream treatments prescribed for psoriasis <sup>11</sup>.

We here apply our uniquely comprehensive set of data to compile the expense incurred by a health care provider for the treatment of psoriasis with NB-UVB based on actual costs, taking into account savings achieved through reduced need for topical psoriasis treatment. Our data represent the actual cost incurred by the provider for all treatment episodes over a period of seven years, including the magnitude of variability associated with distinct staff operating treatment at separate sites, as well as fluctuations occurring over several years. Strikingly, we find that NHS Tayside achieved significant cost savings in drug dispensing in psoriasis patients treated with NB-UVB. In order to make our data generally

applicable, we also detail staff-hours allocated to NB-UVB treatment provision, thereby making local net cost transferable to other health care constellations. Since treatment with NB-UVB phototherapy can reduce the requirement and frequency of costly third line treatments like biologics, our data, suggest that investment in access to NB-UV treatment represents a viable cost-savings measure for health care providers.

## Methods

*Ethics statement:* All data generated in this study were obtained in accordance with the Declaration of Helsinki and in compliance with local governance approval regulations (Caldicot number CSAppJF2101; the use of local Tayside phototherapy data was approved by the National Managed Clinical Network for Phototherapy, Photonet).

*STROBE statement:* This is an observational cohort study. In accordance with the STROBE checklist <sup>12</sup> (see Supplement for full statement).

*Patient cohort:* All methods pertaining to ascertainment of patient cohort, cohort refinement, cohort validation, prescribing data collection and refinement, quantification of psoriasis treatments, extraction of psoriasis-specific drug prescribing, data linkage, definition of NB-UVB treatment episodes, and study design have been described in detail <sup>11</sup>. Statistical analyses shown in figure 2, table 2, and tests were performed using StatPlus software.

*Calculation of prescriptions charges.* The data were accessed from the prescribing reports provided by IDS Scotland (<http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Publications/2016-06-28/2016-06-28-Prescribing-Remuneration-Report.pdf>). For details, see Supplement.)

*Calculation of NB-UVB – incurred cost.* Details of all staff cost are shown in supporting tables. Table S1 contains the number of treatment courses administered at each site throughout the observational period. Table S2 details the precise staff cost for all job roles involved in treatment. Table S3 lists Estates cost. Table S4 calculates the overall treatment cost based on all data. Table S5 lists the summary of staff hours incurred, allowing calculation of costs for other economic regions based on local staff cost. Table S6 details the data used to derive the summary data in Table S5.

## Results

*The cost of topical psoriasis treatment.* We collected data from all consecutive patients registered on the PhotoSys database, limiting analysis to the initial first-ever NB-UVB treatment administered for psoriasis, as described in detail previously <sup>11</sup>. The patient cohort represents a significant fraction of all patients referred for specialist-supervised psoriasis treatment from primary care (n = 1749). As such, this cohort represents a longitudinal sample of patients suffering from moderate-to-severe psoriasis. The fact that they had been referred to secondary care implies that the managing GP assessed control of their disease as inadequate. In Tayside, primary care of psoriasis is limited to the use of topical treatment. Thus, a majority of patients in the cohort is likely to have received the maximal extent of topical treatment available at the time of referral. Table 1 lists the actual cost incurred by the healthcare provider. The combined prescription of all topical treatments between January 2008 and January 2015 amounted to £128 per patient or £35,713 per year. Of note,

despite similar numbers of prescriptions made for steroid-containing creams and 'psoriasis-specific' creams, the latter account for a much higher cost per treatment (£19 vs. £92 per patient, respectively). In psoriasis patients, treatment of their psoriasis amounts to 42 % of all cost spent on prescription drugs (sum of steroid-, psoriasis-specific- and emollient topicals), as shown in Figure 1.

We also analyzed spread and variation of treatment cost incurred per patient. As shown in Figure 2A (top), cost-per-patient was low overall, while increasingly small subgroups of patients generated increasingly high cost. This was also from box plot representation of the data (bottom) which shows that the median cost (yellow) was much lower than the average cost (red), with very few patients representing extreme outliers (green). This is summarised in table 2.

We interrogated the data for evidence of other factors potentially influencing psoriasis-associated drug expenditure, but did not observe any significant differences between patients receiving treatment at different locations, nor was there an effect on cost by patient gender, or age at first NB-UVB treatment (age at diagnosis was not available).

*The impact of NB-UVB on cost of prescription drugs.* We next analysed the cost incurred by NHS Tayside before and after an initial NB-UVB treatment course, respectively, in the 12-months interval prior to, as well as the 12-months interval after treatment (this was set to begin 4 months after initiation of NB-UVB treatment, as described in detail <sup>11</sup>), respectively. As shown in figure 3, there was a statistically significant decrease in the cost of steroid creams and psoriasis-specific topical treatments, both overall annually and per-patient spending. There was no statistically significant change in prescription costs for any of three independent prescriptions classes (hypertension, depression, all



other prescriptions items combined, respectively, Figure 3). Moreover, we have previously shown that the reduction in psoriasis-related prescriptions is not randomly spread among all patients but more pronounced in those patients exhibiting a better treatment outcome of NB-UVB detail <sup>11</sup>, see tables 3 and S1 therein). Therefore, several lines of evidence suggest that the observed changes in drug prescribing- and hence the cost- were unlikely to be merely associated by chance with NB-UVB treatment but much more likely directly caused by the treatment.

Table 3 details savings made following NB-UVB treatment for each of the topical treatment drug classes. The overall savings amounted to £ 50.74 per patient, corresponding to approximately 40% reduction in per-patient prescription drug costs. On an individual level, the actual change in expenditure varied widely between patients. As shown in Figure 4, while most patients achieved cost savings both for steroid and psoriasis-specific topicals, there was a significant minority exhibiting an increase in drug expenditure. As expected, and detailed previously <sup>11</sup>, the number of prescriptions was most markedly reduced in patients who had been recorded as 'clear' or 'minimal residual disease' following NB-UVB treatment, further confirming that net reduction of cost was due to the effect of NB-UVB treatment.

In addition to the drug cost, the NHS incurs a cost for each filled prescription as such. According to IDS-Scotland, these charges are approximately £0.70 per prescription (see Methods). We therefore quantified the number of prescriptions made for each of the topical treatment drug classes. As shown in table 4, there was a significant reduction in prescriptions, amounting to

overall savings of £ 2.48 per patient. Therefore, each NB-UVB-treatment course in Tayside is associated with a net savings of £53.22 in topical treatments cost.

*Staff-related and staff-unrelated cost of NB-UVB treatment.* The cost incurred by NB-UVB treatment involves a number of items including both staff and non-staff related costs. We identified each of these cost components for each of the individual treatment sites analysed (Table 5). Since the actual cost per treatment critically depends on the actual numbers dispensed we also analysed the fluctuation of annual treatment number over the entire observational window (Table S1) and calculated the average cost per treatment by using the average, thereby safeguarding the data against short-term fluctuations. We observed a very low overall variability in treatment number over the entire observational window (Table 5, top row). The staff cost listed in table 5 are not estimates but rather represent the actual staff hours allocated to the various aspects of NB-UVB administration at each of the four sites, as shown in detail in Table S2. The average costs across all sites, both absolute and by relative contribution, are shown in Figure 5. As expected, the costliest component is staff time, accounting for 92 % of cost. “Nurse time” constitutes the largest share, (84 % of total cost, for details, see Table S4, boxed “relative contribution”) where this item includes treatment administration, documentation, data entry, letter dictation, as well as continuous professional training. Furthermore, the staff cost shown in Table 5 includes employer pension, as well as National Insurance contributions, respectively (for details, see Table S2).

*The variability of treatment cost across treatment sites.* Cost of any highly staff-dependent medical treatment could be significantly modified by site-specific factors non-existent in other centres and hence render the resulting data less

informative. Since we had access to site-specific data, we therefore also analysed the variability in cost between separate centres run by distinct staff (table 5). We did not observe an overall trend between large (NW), medium (Perth), and small (St. Andrews, Stracathro) centres, respectively. Rather, variation in cost appear to be primarily related to the number of treatments administered per staff hours. Taking into account the various number of treatments occurring across the four sites between 2008-2015, NHS Tayside spent and average of £253  $\pm$  64 for each NB-UVB course including all overhead costs (Table S4). Given that each treatment lasted an average of 29.7  $\pm$  10.5 sessions<sup>11</sup>, one session generates a cost of £8.50.

*The allocation of staff hours to NB – UVB treatment.* Since the cost for phototherapy is highly salary – dependent, we also listed the actual staff hours required to dispense treatment in an effort to render our data transferable to other economic contexts, as long as local salary scales are known (summarised in Table S5 and detailed in Table S6). One important aspect of this is that treatment is not carried out by single members of staff but spread into job plan components of various staff. For example, even at the smallest treatment site (Stracathro), primary treatment is shared between five local staff, each contributing roughly 20% of their job plan. This set-up may be contribute to overall resilience of service, leading to overall low fluctuation in treatment numbers, as detailed above. One complete NB-UVB course required a total of 0.45  $\pm$  0.14 staff hours, including direct and indirect support roles. By substituting local salary scales, these data allow calculation of analogous cost likely to be incurred by service providers operating in distinct economical contexts.

## Discussion

*The cost of phototherapy:* On average, NHS Tayside spent £257 for each NB-UVB treatment course administered for psoriasis (including all staff overheads) and saved £53. The resulting net average cost of £204 makes this obviously a very economical treatment option. In more general terms, one complete NB-UVB course required an average of  $0.45 \pm 0.14$  staff hours. These figures represent averages across four separate treatment sites and spanning six years, thereby eliminating any spurious fluctuations over time or bias inherent in local factors specific to individual treatment sites. As such, the real cost of NB-UVB contrasts sharply with the previous NICE-UK assignment of £1882 per NB-UVB treatment course <sup>13</sup>. Notably, the actual net expenditure reported here is less than even that of methotrexate cited by NICE based on the BNF drug tariff (£404 per annum <sup>13</sup>).

Our data contrast with previously reported studies. One real-world study from Finland assigned a cost of €755 for a course of NB-UVB with an average of 14 sessions per course <sup>14</sup>. However, it is not clear how the price-charge of €32 per session cited therein related to the cumulative price. In addition, these authors included external items, e.g. lab cost, and arbitrarily levied NB-UVB charges which are not inherent treatment cost but rather form part of an overall profitable pricing structure. Another Finnish-based real-world study from 2009 assigned €39/ annum to methotrexate and €351/annum to acitretin but does not quantify NB-UVB cost, despite stating that this was applied to 36% of patients <sup>15</sup>. One recent U.S.-based review assigned a direct treatment cost of office-based NB-UVB as ranging between \$1414 - \$6676 per course based on three cited

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studies. However, these figures were compiled based on estimates, rather than actual cost and without attempting to explain the huge variability in the cited studies <sup>16</sup>. Again, the notably higher cost, aside from locally varying cost of labor, likely reflects cost accruing within a for-profit business model. Even in England, which still has a national health service, services such as phototherapy are not evaluated on the basis of real cost but assigned tariffs. For phototherapy, the assumed tariff is £74 per session for patients older than 13 and £86 for 12 years and younger <sup>17</sup> (sheet 1a APC & OPROC 17.18., codes JC47A and JC47B), with is in striking contrast with the actual cost (£8.50 per session, see above). Clearly, this would constitute a disincentive to provide treatment. Numerous other health economic studies focusing primarily on more expensive biologics have assigned a cost to NB-UVB as a comparator treatment. However, these studies generally focus on “cost per PASI75”, using data from controlled trials rather than real-world direct cost, as detailed here. Thus, the data reported here, to the best of our knowledge, represent the most comprehensive direct measurement of actual cost accrued for NB-UVB treatment to date.

Importantly, It should be noted that the cost of NB-UVB we describe here does not come at the price of reduced efficacy. Rather, we recently documented that NB-UVB is highly effective in psoriasis under real-world conditions <sup>11</sup>. Taking together available evidence, NB-UVB is not only effective but by far the most economical treatment option for psoriasis inadequately controlled with topical treatments, perhaps with the exception of methotrexate. In contrast to NB-UVB, however, methotrexate is associated with a number of adverse events, as we have recently quantified both in clinical trials and under real world conditions <sup>10, 18</sup>. In conjunction with our analysis of the efficacy of NB-UVB <sup>11</sup>, our data

therefore dispel a widely held implicit notion that NB-UVB is expensive (as reflected in the NICE statement cited above) and ineffective. As such, from the perspective of health care provision, extending access to and widening the implementation of NB-UVB deserves serious consideration.

*Limitations:* The present study has a number of obvious limitations. Firstly, we only included initial NB-UVB-courses and only those administered for psoriasis, as dictated by the study design <sup>11</sup>. Secondly, we did not consider other phototherapy applications, especially PUVA, which are commonly offered by the same centres. Third, we did not consider non-provider cost by patients (or employers), including travel and absence from work (for indicative data on the latter, see <sup>9</sup>). Such costs can be reduced by provision of a comprehensive phototherapy service including home phototherapy<sup>19, 20</sup> and patient self-administration phototherapy<sup>21</sup> for those who cannot readily attend the hospital units (which must have adequate opening hours). Fourthly, we did not perform health economic modelling, such as, e.g., modelling of treatment outcomes to derive QALY-related cost. Finally, our analysis provides direct cost only for the UK NHS-based hospital context. However, we have provided detailed functional staff-hour allocation which we hope will enable readers to translate cost into other salary-contexts (see below).

*Cost of topical treatment in psoriasis:* In the course of this study we also define the actual cost associated with topical treatment for psoriasis on a population level. Thus, in Tayside, Scotland, treatment with creams for psoriasis accounts for 42 % of the total cost incurred by patients with disease of sufficient severity to warrant referral to secondary care (Figure 1). The actual annual cost of these creams (£128, Table 2) is much lower than the NICE – UK estimate <sup>13</sup>,

possibly reflecting the previously noted relative under – treatment of psoriasis under real world conditions. By way of comparison, the data in Table 1 show that the cost incurred per patient for psoriasis drugs is commensurate to the per-patient treatment cost for hypertension in patients requiring three different hypertensive agents and a nurse specialist review<sup>22</sup>. It is remarkable, therefore, that this cost is reduced by an average of approximately 40 % over the 12-months interval following NB-UVB treatment. To the best of our knowledge, this is the only psoriasis treatment confirmed to incur directly proven significant net savings in topical treatment cost to date. Of note, our data show a non-Gaussian distribution of cost (Figure 2) which should inform future model development. Moreover, the cost of topical treatment for psoriasis, as detailed here, represents a comprehensive real-world population sample, as opposed to a treatment cohort subject to selection and reporting bias, as discussed previously<sup>11</sup>. Therefore, these data (Table 2) should prove valuable to regulating bodies, such as NICE, when estimating cost effectiveness for alternative treatments.

*Indirect savings of NB-UVB:* The actual cost of NB-UVB in every day practice is likely to be even lower than reported here for three reasons. Firstly, the average efficacy, and thus indirect savings in topical creams are likely even more pronounced in subsequent NB-UVB courses, since patients experiencing no or limited benefit in the initial treatment episode are less likely to undergo repeat treatment, thereby introducing a bias toward greater relative efficacy. Secondly, the number of outpatient visits and GP reviews are likely also reduced. Thirdly, administration of 3rd line systemic or biologic treatments will be delayed, or even avoided, in some patients, adding further savings.

*Added benefits of providing NB-UVB:* Although considered here for psoriasis, NB-UVB is also efficacious in other conditions. For example, oral systemic treatments for pruritic dermatoses often prove ineffective in establishing symptomatic control. Our data illustrate that anti-histamine consumption is reduced following administration of NB-UVB, even in psoriasis patients <sup>11</sup>, in confirmation of the widespread observation that NB-UVB is effective to control pruritus <sup>23, 24</sup>. Other common conditions, notably eczema <sup>25, 26</sup> and urticaria <sup>27</sup>, also show good response to this treatment, thereby adding to indirect net savings by creating synergy on staff and equipment cost.

*The cost of newly establishing access to NB-UVB:* How much would it cost to newly establish access to NB-UVB locally? The data provided in Tables S5 and S6 allow calculation of cost faced by providers when setting up or extending NB-UVB treatment facilities. For example, the small treatment centre in Stracathro allocates 33h per week, distributed to 20% of a 40h work-week among four nurses, respectively, to run the service, thus allowing sufficient cross-cover for staff absence. Consultant and other medical supervision is allocated at 1h / week; equipment/ maintenance/ estate cost need to be added but are of lesser cost implication. Using the NHS salary costs (Table S2) the entire staff-cost package, including pension/insurance contribution, for this site amounts to £ 30,750 per year, in return for a total of 152 NB-UVB and 81 PUVA treatment courses. The staff cost can be readily adapted to local salary scales using the staff hour breakdown given in table S6. Even in health care systems where the additional savings gained through reduced drug treatments (£53 per treatment) are not allocated to the NB-UVB service provider, and allowing for added cost for implementation, both set-up and running costs are recouped by



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delaying the need to prescribe biologic treatment by one year in as few as three patients (Scottish Medicines Consortium cost template, <sup>28</sup>). It is also worth pointing out that Tayside, Scotland, is a very rural clinical setting, requiring patients to travel comparatively large distances in order to attend for treatment with relatively large impact on loss of work hours. It is likely that patient acceptance and compliance will be even easier to achieve in urban areas. Given the added benefits of this service, our data suggest that implementation of NB-UVB service not only offers effective treatment, but may be highly attractive in economic terms for providers.

*Position of NB-UVB in psoriasis treatment pathways.* The efficacy and cost- effectiveness of NB-UVB treatment is difficult to reconcile with its position in various current psoriasis treatment guidelines. Thus, the current British Association of Dermatologist (BAD) guidelines do not even consider NB-UVB on the pathway to Biologics treatment <sup>6</sup>. Similarly, many guidelines consider NB-UVB as a treatment option but not one which should be actively encouraged. In these cases, safety is cited as a reason to discourage treatment. Thus, the updated Canadian guidelines state: “it has not been established whether NB-UVB is carcinogenic in humans; however, speculation based on nonclinical data suggests that NB-UVB could be more carcinogenic than natural [...] sunlight. [...] in the absence of [safety] evidence, it is prudent [...] to reduce exposure to NB-UVB radiation.”<sup>29</sup> Similarly, the Spanish guidelines erroneously equate NB-UVB with PUVA, by stipulating that Biologics may be used in patients “at risk of toxicity with [...] phototherapy” <sup>30</sup>, while obviously drug toxicity is known only for PUVA but entirely absent in NB-UVB. The current guidelines of the U.S. American Academy of Dermatology also do not even suggest that NB – UVB

ought to be actively considered before moving to systemic treatments. Likewise, the U.S. National Psoriasis Foundation actively opposes any effort to apply cost-effective treatments ahead of more expensive alternatives (called “step therapy”), lobbying actively for legislation to ban this approach. Clearly, NB-UVB poses significant obstacles, not measured here, including non-provider costs including travel and absence from work, time commitment and scheduling difficulties. These issues will limit practical use in many cases. These limitations notwithstanding, treatment recommendations on psoriasis in many countries do not reflect the efficacy of NB – UVB analysis <sup>11</sup>, nor its cost effectiveness. The data presented here provide a rationale to review such guidelines.

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#### References

1. Gupta G, Long J, Tillman DM. The efficacy of narrowband ultraviolet B phototherapy in psoriasis using objective and subjective outcome measures. The British journal of dermatology. 1999 May;140(5):887-90. PubMed PMID: 10354027.
2. Cameron H, Dawe RS, Yule S, et al. A randomized, observer-blinded trial of twice vs. three times weekly narrowband ultraviolet B phototherapy for chronic plaque psoriasis. The British journal of dermatology. 2002 Nov;147(5):973-8. PubMed PMID: 12410709.
3. Dawe RS, Wainwright NJ, Cameron H, Ferguson J. Narrow-band (TL-01) ultraviolet B phototherapy for chronic plaque psoriasis: three times or five times weekly treatment? The British journal of dermatology. 1998 May;138(5):833-9. PubMed PMID: 9666830.

4. Green C, Lakshmipathi T, Johnson BE, Ferguson J. A comparison of the efficacy and relapse rates of narrowband UVB (TL-01) monotherapy vs. etretinate (re-TL-01) vs. etretinate-PUVA (re-PUVA) in the treatment of psoriasis patients. *The British journal of dermatology*. 1992 Jul;127(1):5-9. PubMed PMID: 1637696.
5. Green C, Ferguson J, Lakshmipathi T, Johnson BE. 311 nm UVB phototherapy--an effective treatment for psoriasis. *The British journal of dermatology*. 1988 Dec;119(6):691-6. PubMed PMID: 3203066.
6. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. *The British journal of dermatology*. 2017 May 17. PubMed PMID: 28513835.
7. Langan SM, Heerey A, Barry M, Barnes L. Cost analysis of narrowband UVB phototherapy in psoriasis. *Journal of the American Academy of Dermatology*. 2004 Apr;50(4):623-6. PubMed PMID: 15034514.
8. Yentzer BA, Gustafson CJ, Feldman SR. Explicit and implicit copayments for phototherapy: examining the cost of commuting. *Dermatology online journal*. 2013 Jun 15;19(6):18563. PubMed PMID: 24011313.
9. Koek MB, Sigurdsson V, van Weelden H, et al. Cost effectiveness of home ultraviolet B phototherapy for psoriasis: economic evaluation of a randomised controlled trial (PLUTO study). *Bmj*. 2010 Apr 20;340:c1490. PubMed PMID: 20406865. Pubmed Central PMCID: 2857750.
10. West J, Ogston S, Palmer C, et al. Methotrexate in psoriasis under real-world conditions: long-term efficacy and tolerability. *The British journal of dermatology*. 2016 Jun;174(6):1407-10. PubMed PMID: 26852010.
11. Foerster J BK, West J, Cameron H, Fleming C, Ibbotson S, Dawe R. Narrowband UVB treatment is highly effective and causes a strong reduction in the use of steroid and other creams in psoriasis patients in clinical practice. *PloS one*. 2017. Epub August 3, 2017.
12. Editors TPM. Observational Studies: Getting Clear about Transparency. *PLoS Med*. 2014;11(8):e1001711.
13. NICE. Clinical guideline 2012 2012. Available from: <https://http://www.nice.org.uk/guidance/cg153/resources/costing-report-188311357>.

14. Mustonen A, Leino M, Mattila K, et al. Treatment costs of psoriasis in a tertiary-level clinic. *BMC health services research*. 2014 Aug 15;14:344. PubMed PMID: 25128268. Pubmed Central PMCID: 4141106.
15. Mustonen A, Mattila K, Leino M, et al. The costs of psoriasis medications. *Dermatology and therapy*. 2013 Dec;3(2):169-77. PubMed PMID: 24338674. Pubmed Central PMCID: 3889304.
16. Brezinski EA, Dhillon JS, Armstrong AW. Economic Burden of Psoriasis in the United States: A Systematic Review. *JAMA dermatology*. 2015 Jun;151(6):651-8. PubMed PMID: 25565304.
17. West J, Ogston S, Foerster J. Safety and Efficacy of Methotrexate in Psoriasis: A Meta-Analysis of Published Trials. *PloS one*. 2016;11(5):e0153740. PubMed PMID: 27168193. Pubmed Central PMCID: 4864230.
18. Cameron H, Yule S, Moseley H, et al. Taking treatment to the patient: development of a home TL-01 ultraviolet B phototherapy service. *The British journal of dermatology*. 2002 Nov;147(5):957-65. PubMed PMID: 12410707.
19. Cameron H, Yule S, Dawe RS, et al. Review of an established UK home phototherapy service 1998-2011: improving access to a cost-effective treatment for chronic skin disease. *Public health*. 2014 Apr;128(4):317-24. PubMed PMID: 24726005.
20. Yule S, Sanyal S, Ibbotson S, et al. Self-administration of hospital-based narrowband ultraviolet B (TL-01) phototherapy: a feasibility study in an outpatient setting. *Br J Dermatol*. 2013 Aug;169(2):464-8. PubMed PMID: 23488569.
21. Sheppard JP, Fletcher K, McManus RJ, Mant J. Prevalence and costs of treating uncomplicated stage 1 hypertension in primary care: a cross-sectional analysis. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2014 Oct;64(627):e641-8. PubMed PMID: 25267050. Pubmed Central PMCID: 4173727.
22. Chan IH, Murrell DF. Itch Management: Physical Approaches (UV Phototherapy, Acupuncture). *Current problems in dermatology*. 2016;50:54-63. PubMed PMID: 27578072.
23. Powell JB, Gach JE. Phototherapy in the elderly. *Clinical and experimental dermatology*. 2015 Aug;40(6):605-10. PubMed PMID: 25809797.

24. Patrizi A, Raone B, Ravaioli GM. Management of atopic dermatitis: safety and efficacy of phototherapy. *Clinical, cosmetic and investigational dermatology*. 2015;8:511-20. PubMed PMID: 26491366. Pubmed Central PMCID: 4599569.
25. Garritsen FM, Brouwer MW, Limpens J, Spuls PI. Photo(chemo)therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. *The British journal of dermatology*. 2014 Mar;170(3):501-13. PubMed PMID: 24116934.
26. Aydogan K, Karadogan SK, Tunali S, Saricaoglu H. Narrowband ultraviolet B (311 nm, TL01) phototherapy in chronic ordinary urticaria. *International journal of dermatology*. 2012 Jan;51(1):98-103. PubMed PMID: 22182386.
27. Consortium SM. Advice on Ixekizumab 2017. Available from: [https://http://www.scottishmedicines.org.uk/files/advice/ixekizumab\\_Taltz\\_FINAL\\_March\\_2017\\_Amended\\_05.04.17\\_for\\_website.pdf](https://http://www.scottishmedicines.org.uk/files/advice/ixekizumab_Taltz_FINAL_March_2017_Amended_05.04.17_for_website.pdf).
28. Canadian Psoriasis Guidelines Addendum C. 2016 Addendum to the Canadian Guidelines for the Management of Plaque Psoriasis 2009. *Journal of cutaneous medicine and surgery*. 2016 Sep;20(5):375-431. PubMed PMID: 27421294. Pubmed Central PMCID: 5014087.
29. Dauden E, Puig L, Ferrandiz C, et al. Consensus document on the evaluation and treatment of moderate-to-severe psoriasis: Psoriasis Group of the Spanish Academy of Dermatology and Venereology. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2016 Mar;30 Suppl 2:1-18. PubMed PMID: 26812550.

## Tables

Table 1. Cost incurred by NHS Tayside for psoriasis-associated treatment in primary care<sup>1</sup>

Drug class	Nr of patients on treatment	Cost (£)	
		Per patient	Per year (all patients)
Pso-specifics creams <sup>3</sup>	1461	92	21512
Steroid-creams	1287	19	3913
Emollients	1262	17	3434
Systemic treatments <sup>4</sup>	55	3.6	32
All psoriasis – related scripts		132	28890
Anti-depressives	301	7.7	371
Anti-hypertensives	334	7.3	390
Anti-histamines	46	1.4	10
All other prescriptions	1626	161	41897
All psoriasis – unrelated scripts		177	42668

<sup>1</sup>Data represent all prescriptions made out for psoriasis patients referred for secondary care treatment and subsequently receiving NB-UVB treatment between January 2008 and January 2015 (N = 1749, see Methods).

<sup>2</sup> Sum of steroid-containing-, psoriasis-specific- and emollient topical prescriptions.

<sup>3</sup>Defined by British National Formulary code 13.5.2 for topical agents indicated solely for psoriasis (e.g. calcipotriol, dithranol, coal tar), as detailed in <sup>11</sup>.

<sup>4</sup>Prescriptions for methotrexate (n = 271), acitretin (n = 10), and cyclosporine (n = 5).

Table 2. Distribution of cost for topical psoriasis treatment in NHS Tayside.<sup>1</sup>

Annual Cost/ patient	Steroid Creams	Pso-specific Topicals	Emollients
Cost (£)			
Average $\pm$ s.d.	26 $\pm$ 29	109 $\pm$ 111	23 $\pm$ 27
Median	16	73	13
75% percentile	32	139	27
Top outlier	249	920	226

<sup>1</sup>Data shown detail cost for those patients receiving steroid cream (n = 1287), topical psoriasis cream treatments (n = 1461), or emollient cream treatment (n = 1262), respectively.

Table 3. Cost reduction for topical psoriasis treatments after NB-UVB treatment<sup>1</sup>

	<b>Steroid creams</b>	<b>Psoriasis- Specifics</b>	<b>Emollients</b>	<b>All topicals</b>
Average per patient	£ 7.43	£ 39.26	£ 4.05	£ 50.74
Median per patient	£ 3.81	£ 29.46	£ 1.61	£ 34.88
Annual <sup>2</sup>	£ 2079	£ 10987	£ 1133	£ 14199

<sup>1</sup>Annual reduction in cost for drug prescriptions for psoriasis after one single course of NB-UVB phototherapy. For details see text.

<sup>2</sup>Annual savings are calculated for 12 months out of the total 75 months observational window. Within the entire cohort (n = 1749), this number is equivalent to savings made for n = 280 patients.



Table 4. Change in the number of prescriptions made out for psoriasis before versus after NB-UVB treatment.<sup>1</sup>

Cost of prescriptions (£)	per year			per patient		
	Before	After	Savin	Before	After	Savin
	UV	UV	gs	UV	UV	gs
<b>Steroids</b>	854	495	250	3.05	1.77	0.90
<b>Pso-Topicals</b>	998	562	304	3.56	2.01	1.09
<b>Emollients</b>	762	566	137	2.72	2.02	0.49
<b>All scripts</b>	2613	1623	692	9.34	5.80	2.48

<sup>1</sup>Numbers shown are the absolute incurred prescription fees incurred by NHS Tayside as remuneration for pharmacies for filling prescription made out for all psoriasis patients (n = 1749) in the 12-month interval before, or after NB-UVB treatment, respectively, calculated for treatments occurring within a single year, or per patient, as shown in the table (for details see Methods).

Table 5. The cost of NB-UVB treatment in NHS Tayside.<sup>1</sup>

	Dundee	Perth	Stracathro	St. Andrews
Centre size	Large	Medium	Small	Small
Courses administered <sup>2</sup>	430 ± 22	233 ± 24	112 ± 11	130 ± 15
<b>Staff – related costs<sup>3</sup></b>				
Photobiology technician	19	1	1	1
Nurse <sup>4</sup>	203	260	123	232
Administrative support <sup>5</sup>	5	2	1.4	1.8
Consultant supervision <sup>6</sup>	31	3	6	7
Non-consultant clinician <sup>7</sup>	8	7	3	
<b>Non staff – related costs</b>				
Equipment <sup>7</sup>	7	7	12	14
Medical Physics <sup>8</sup>	1	2		
Estate <sup>9</sup>	0.04	0.05	0.08	0.1
<b>Total</b>	<b>274</b>	<b>282</b>	<b>145</b>	<b>256</b>

<sup>1</sup>Data show the cost incurred per treatment course rounded to the nearest £ (see table S4)

<sup>2</sup> Average ± s.d. between 2010 – 2015. One course consists of 30 ± 10 (average ± s.d.) treatment sessions, with minimal variation between the four different centers, as previously shown (<sup>11</sup>, Figure 5d therein).

<sup>3</sup>For salary components, including indirect cost (pension and National insurance cost), see Table S2.

<sup>4</sup>Cost includes staff hours allocated to treatment administration, documentation, data entry, letter dictation, continuous professional training. Data shown are derived from salary scales detailed in Table S2 for each of the centres.

<sup>5</sup>Secreterial support, numbers shown cover staff hours allocated to typing and appointment booking.

<sup>6</sup>Includes staff hours by both consultant and registrars allocated to phototherapy as per job plan (see Table S6).

<sup>7</sup>Based on purchasing price of £1603 as directly incurred by NHS Tayside in 2015 for one NB-UVB cabinet including depreciation, average lifetime, replacement kit (bulbs). Cost of two units used for the Dundee site (Ninewells hospital).

<sup>8</sup>Includes maintenance, lamp calibration, as provided by Medical Physics.

<sup>9</sup>Based on published cost for cleaning, property maintenance, energy, and rates per m<sup>2</sup>. in NHS Tayside (for details see table S3).

## Supporting Information

File: "Supplement".

This file contains the extended STROBE information as well as details on procuring data on drug prescription costs.

File: "Table S1 – S6".

This file contains detailed information on the number and cost of NB – UVB treatment courses administered across all treatment sites in Tayside / Scotland during the observational window.

## Legends to Figures

Figure 1. Relative contribution of prescribed drugs to overall treatment cost incurred by NHS Tayside for psoriasis patients between January 2008 and January 2015. Numbers shown represent the percent of total (100 % = £ 86,493 per year, see Table 1). H1- antihistamines, Depr- anti-depressive drugs, HTN- antihypertensives. The definition 'Pso-creams' refers to topical treatments only prescribable for psoriasis in the British National Formulary (BNF code 13.5.2) and comprises calcipotriol, calcipotriol with betamethasone, calcitriol, coal tar products, dithranol, salicylic acid compounds, tacalcitol, as well as tazarotene.

Figure 2. The distribution of cost for topical psoriasis treatments in primary care in Scotland. Top: Histogram plots for all patients (n = 1749) incurring annual

costs up to the threshold amounts given in £ on the x-axis for each of the drug classes indicated. Bottom: Box plots showing percentiles, median, average costs, as well as distribution of outliers, as indicated in the color coded lines.

Figure 3. The effect of an initial course of NB-UVB treatment on the cost of prescription for topical psoriasis medicines. The figure shows the total cost incurred by NHS Tayside, expressed in £ before (dark shaded), and after (light shaded) NB-UVB treatment, respectively. Top: cost per annum for all patients, Bottom: annual cost per patient. \*  $p < 0.01$  in a paired t-test. Depr- antidepressive drugs, HTN- antihypertensive drugs

Figure 4. The distribution of change in cost for drugs prescribed for psoriasis after versus before one course of NB-UVB phototherapy. Histograms show the actual change in cost (given in £) across all patients for the drug class indicated at the top of each plot.

Figure 5. The cost of administering NB-UVB phototherapy in Tayside, Scotland. (A) Actual cost shown as average  $\pm$  s.d. of costs incurred across individual sites, as detailed in Table 5. Cost are shown on a log-scale so as to visualise both high- and low-cost components, respectively. (B) Pie chart illustrating the percentage contribution of each cost component shown in (A) where actual percent cost are shown for each item.

## References

1. Gupta G, Long J, Tillman DM. The efficacy of narrowband ultraviolet B phototherapy in psoriasis using objective and subjective outcome measures. The British journal of dermatology. 1999 May;140(5):887-90. PubMed PMID: 10354027.

2. Cameron H, Dawe RS, Yule S, et al. A randomized, observer-blinded trial of twice vs. three times weekly narrowband ultraviolet B phototherapy for chronic plaque psoriasis. *The British journal of dermatology*. 2002 Nov;147(5):973-8. PubMed PMID: 12410709.
3. Dawe RS, Wainwright NJ, Cameron H, Ferguson J. Narrow-band (TL-01) ultraviolet B phototherapy for chronic plaque psoriasis: three times or five times weekly treatment? *The British journal of dermatology*. 1998 May;138(5):833-9. PubMed PMID: 9666830.
4. Green C, Lakshmipathi T, Johnson BE, Ferguson J. A comparison of the efficacy and relapse rates of narrowband UVB (TL-01) monotherapy vs. etretinate (re-TL-01) vs. etretinate-PUVA (re-PUVA) in the treatment of psoriasis patients. *The British journal of dermatology*. 1992 Jul;127(1):5-9. PubMed PMID: 1637696.
5. Green C, Ferguson J, Lakshmipathi T, Johnson BE. 311 nm UVB phototherapy--an effective treatment for psoriasis. *The British journal of dermatology*. 1988 Dec;119(6):691-6. PubMed PMID: 3203066.
6. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. *The British journal of dermatology*. 2017 May 17. PubMed PMID: 28513835.
7. Langan SM, Heerey A, Barry M, Barnes L. Cost analysis of narrowband UVB phototherapy in psoriasis. *Journal of the American Academy of Dermatology*. 2004 Apr;50(4):623-6. PubMed PMID: 15034514.
8. Yentzer BA, Gustafson CJ, Feldman SR. Explicit and implicit copayments for phototherapy: examining the cost of commuting. *Dermatology online journal*. 2013 Jun 15;19(6):18563. PubMed PMID: 24011313.
9. Koek MB, Sigurdsson V, van Weelden H, et al. Cost effectiveness of home ultraviolet B phototherapy for psoriasis: economic evaluation of a randomised controlled trial (PLUTO study). *Bmj*. 2010 Apr 20;340:c1490. PubMed PMID: 20406865. Pubmed Central PMCID: 2857750.
10. West J, Ogston S, Palmer C, et al. Methotrexate in psoriasis under real-world conditions: long-term efficacy and tolerability. *The British journal of dermatology*. 2016 Jun;174(6):1407-10. PubMed PMID: 26852010.
11. Foerster J BK, West J, Cameron H, Fleming C, Ibbotson S, Dawe R. Narrowband UVB treatment is highly effective and causes a strong reduction in the use of steroid and other creams in psoriasis patients in clinical practice. *PloS one*. 2017. Epub August 3, 2017.
12. Editors TPM. *Observational Studies: Getting Clear about Transparency*. *PLoS Med*. 2014;11(8):e1001711.
13. NICE. Clinical guideline 2012 2012. Available from: <https://www.nice.org.uk/guidance/cg153/resources/costing-report-188311357>.
14. Mustonen A, Leino M, Mattila K, et al. Treatment costs of psoriasis in a tertiary-level clinic. *BMC health services research*. 2014 Aug 15;14:344. PubMed PMID: 25128268. Pubmed Central PMCID: 4141106.
15. Mustonen A, Mattila K, Leino M, et al. The costs of psoriasis medications. *Dermatology and therapy*. 2013 Dec;3(2):169-77. PubMed PMID: 24338674. Pubmed Central PMCID: 3889304.
16. Brezinski EA, Dhillon JS, Armstrong AW. Economic Burden of Psoriasis in the United States: A Systematic Review. *JAMA dermatology*. 2015 Jun;151(6):651-8. PubMed PMID: 25565304.
17. Improvement-NHS. NHS England 2017-2018 Tariff 2017. Available from: [https://improvement.nhs.uk/.../Copy\\_of\\_Annex\\_A\\_-\\_National\\_tariff\\_workbook.xlsx](https://improvement.nhs.uk/.../Copy_of_Annex_A_-_National_tariff_workbook.xlsx).

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18. West J, Ogston S, Foerster J. Safety and Efficacy of Methotrexate in Psoriasis: A Meta-Analysis of Published Trials. *PloS one*. 2016;11(5):e0153740. PubMed PMID: 27168193. Pubmed Central PMCID: 4864230.
  19. Cameron H, Yule S, Moseley H, et al. Taking treatment to the patient: development of a home TL-01 ultraviolet B phototherapy service. *The British journal of dermatology*. 2002 Nov;147(5):957-65. PubMed PMID: 12410707.
  20. Cameron H, Yule S, Dawe RS, et al. Review of an established UK home phototherapy service 1998-2011: improving access to a cost-effective treatment for chronic skin disease. *Public health*. 2014 Apr;128(4):317-24. PubMed PMID: 24726005.
  21. Yule S, Sanyal S, Ibbotson S, et al. Self-administration of hospital-based narrowband ultraviolet B (TL-01) phototherapy: a feasibility study in an outpatient setting. *Br J Dermatol*. 2013 Aug;169(2):464-8. PubMed PMID: 23488569.
  22. Sheppard JP, Fletcher K, McManus RJ, Mant J. Prevalence and costs of treating uncomplicated stage 1 hypertension in primary care: a cross-sectional analysis. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2014 Oct;64(627):e641-8. PubMed PMID: 25267050. Pubmed Central PMCID: 4173727.
  23. Chan IH, Murrell DF. Itch Management: Physical Approaches (UV Phototherapy, Acupuncture). *Current problems in dermatology*. 2016;50:54-63. PubMed PMID: 27578072.
  24. Powell JB, Gach JE. Phototherapy in the elderly. *Clinical and experimental dermatology*. 2015 Aug;40(6):605-10. PubMed PMID: 25809797.
  25. Patrizi A, Raone B, Ravaoli GM. Management of atopic dermatitis: safety and efficacy of phototherapy. *Clinical, cosmetic and investigational dermatology*. 2015;8:511-20. PubMed PMID: 26491366. Pubmed Central PMCID: 4599569.
  26. Garritsen FM, Brouwer MW, Limpens J, Spuls PI. Photo(chemo)therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. *The British journal of dermatology*. 2014 Mar;170(3):501-13. PubMed PMID: 24116934.
  27. Aydogan K, Karadogan SK, Tunali S, Saricaoglu H. Narrowband ultraviolet B (311 nm, TL01) phototherapy in chronic ordinary urticaria. *International journal of dermatology*. 2012 Jan;51(1):98-103. PubMed PMID: 22182386.
  28. Consortium SM. Advice on Ixekizumab 2017. Available from: [https://http://www.scottishmedicines.org.uk/files/advice/ixekizumab\\_Taltz\\_FINAL\\_March\\_2017\\_Amended\\_05.04.17\\_for\\_website.pdf](https://http://www.scottishmedicines.org.uk/files/advice/ixekizumab_Taltz_FINAL_March_2017_Amended_05.04.17_for_website.pdf).
  29. Canadian Psoriasis Guidelines Addendum C. 2016 Addendum to the Canadian Guidelines for the Management of Plaque Psoriasis 2009. *Journal of cutaneous medicine and surgery*. 2016 Sep;20(5):375-431. PubMed PMID: 27421294. Pubmed Central PMCID: 5014087.
  30. Dauden E, Puig L, Ferrandiz C, et al. Consensus document on the evaluation and treatment of moderate-to-severe psoriasis: Psoriasis Group of the Spanish Academy of Dermatology and Venereology. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2016 Mar;30 Suppl 2:1-18. PubMed PMID: 26812550.



